PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 9/70, 47/14, 47/10	A1	(11) International Publication Number: WO 93/23019 (43) International Publication Date: 25 November 1993 (25.11.93)

(21) International Application Number: PCT/US93/04442

(22) International Filing Date: 10 May 1993 (10.05.93)

(30) Priority data:
07/881,104 11 May 1992 (11.05.92) US
08/014,922 8 February 1993 (08.02.93) US

(71) Applicant: SRI INTERNATIONAL [US/US]; 333 Ravenswood Avenue, Menlo Park, CA 94025-3493 (US).

(72) Inventors: FRIEND, David, R. ; 454 Ninth Avenue, Menlo Park, CA 94025 (US). NOLEN, Harold, W., III ; 3028 Via Del Coronado, San Jose, CA 95132 (US). CATZ, Paul, G. ; 3332 Emerson Street, Palo Alto, CA 94306 (US).

(74) Agents: CLARK, Janet, Pauline; SRI International, 333 Ravenswood Avenue, Menlo Park, CA 94025-3493 (US) et al.

(81) Designated States: CA, JP, KR, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: TRANSDERMAL DRUG DELIVERY SYSTEMS AND RELATED COMPOSITIONS AND METHODS OF USE

(57) Abstract

Transdermal drug delivery systems are provided in which a release rate-controlling means limits the flux of drug out of the device but not the flux of skin permeation enhancer. The devices contain an enhancer composition of a lower aliphatic ester of a lower aliphatic carboxylic acid, a lower alkanol, and, optionally, additional permeation enhancing components. Methods for using the transdermal systems for administering pharmacologically active agents are provided as well.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NL	Netherlands
BE	Belgium	GN	Guinea	NO	Norway
BF	Burkina Faso	GR	Greece	NZ	New Zealand
BG	Bulgaria	HU	Hungary	PL	Poland
BJ	Benin	IE	Ireland	PT	Portugal
BR	Brazil	IT	Italy	RO	Romania
CA	Canada	JP	Japan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo			SE	Sweden
CH	Switzerland	KR	Republic of Korea	SK	Slovak Republic
CI	Côte d'Ivoire	KZ	Kazakhstan	SN	Senegal
CM	Cameroon	LI	Liechtenstein	SU	Soviet Union
CS	Czechoslovakia	LK	Sri Lanka	TD	Chad
CZ	Czech Republic	LU	Luxembourg	TG	Togo
DE	Germany	MC	Monaco	UA	Ukraine
DK	Denmark	MG	Madagascar	US	United States of America
ES	Spain	ML	Mali	VN	Viet Nam
FI	Finland	MN	Mongolia		

TRANSDERMAL DRUG DELIVERY SYSTEMS AND RELATED COMPOSITIONS AND METHODS OF USE

Technical Field

The present invention relates generally to the transdermal administration of pharmacologically active agents, and more particularly relates to novel transdermal drug delivery systems and methods of administering drugs using such systems.

Background

The delivery of drugs through the skin provides many advantages; primarily, such a means of delivery is a comfortable, convenient, and noninvasive way of administering drugs. The variable rates of absorption and metabolism encountered in oral treatment are avoided, and other inherent inconveniences--*e.g.*, gastrointestinal irritation and the like--are eliminated as well. Transdermal drug delivery also makes possible a high degree of control over blood concentrations of any particular drug.

Skin is a structurally complex, relatively thick membrane. Molecules moving from the environment into and through intact skin must first penetrate the stratum corneum and any material on its surface. The molecules must then penetrate the viable epidermis, the papillary dermis, and the capillary walls into the blood stream or lymph channels. To be so absorbed, molecules must overcome a different resistance to penetration in each type of tissue. Transport across the skin membrane is thus a complex phenomenon. However, it is the cells of the stratum corneum which present the primary barrier to absorption of topical compositions or transdermally administered drugs. The stratum corneum is a thin layer of dense, highly keratinized cells approximately 10-15 microns thick over most of the body.

In order to increase skin permeability, and in particular to increase the permeability of the stratum corneum (*i.e.*, so as to achieve enhanced penetration, through the skin, of the drug to be administered transdermally), the skin may be pretreated with a penetration enhancing agent (or "permeation enhancer," as sometimes referred to herein) prior to application of a drug. Alternatively, and preferably, a drug and a permeation enhancer are delivered concurrently.

The present invention is directed to a novel composition for enhancing the penetration of pharmacologically active agents through skin, the composition based on (1) a lower aliphatic ester of a lower aliphatic carboxylic acid with (2) a lower alkanol. The enhancer compositions of the invention have been found by the inventors herein to be particularly effective in enhancing the penetration of pharmaceutically active agents through skin, and surprisingly more effective than either component of the composition when used alone.

While there are a number of patents and publications available which relate to the transdermal administration of drugs and to skin permeation enhancer compositions, applicants are unaware of any art which suggests that the combinations now disclosed herein provide a synergistic enhancing effect.

The present invention is directed to novel transdermal drug delivery systems in which the penetration of pharmacologically active agents through skin is enhanced by co-administering drug with a permeation enhancing composition as described in copending, commonly assigned U.S. Patent Application Serial No. 07/783,480, filed 28 October 1991, the disclosure of which is hereby incorporated by reference in its entirety. Briefly, the enhancer compositions described in the aforementioned application contain (1) a lower aliphatic ester of a lower aliphatic carboxylic acid, (2) a lower alkanol, and (3) optionally, additional permeation enhancing components such as a lower aliphatic ester of a higher carboxylic acid (*e.g.*, isopropyl myristate). Such enhancer compositions were found to be surprisingly more effective than either component of the composition used alone.

The drug delivery systems disclosed herein make use of such a permeation enhancer composition, in a device containing a release rate-controlling means which controls the flow of drug out of the device but not the flow of permeation enhancer. That is, the devices contain specifically formulated polymer membranes which do not limit the rate of enhancer delivery in any way-- so that the delivery of solvent is skin rate-controlled-- but which provide for a steady-state flux of drug out of the device, *i.e.*, release rate of drug is "system-controlled." Although there are a number of patents and literature references which relate to rate-controlling membranes in transdermal drug delivery systems, as will be summarized in the next section herein, applicants are unaware of any art which describes a rate-controlling means that selectively meters the flow of drug but not the flow of enhancer.

The present systems are particularly useful in the transdermal administration of the angiotensin converting enzyme (ACE) inhibitor drug captopril, the beta blocker timolol, and the narcotic analgesics buprenorphine and nalbuphine.

Related Art

The following references relate to one or more aspects of the present invention.

Skin permeation enhancers, generally: Various compounds for enhancing the permeability of skin are known in the art. U.S. Patent Nos. 4,006,218, 3,551,554, and 3,472,931, for example, respectively describe the use of dimethylsulfoxide (DMSO), dimethylformamide (DMF) and N,N-dimethylacetamide (DMA) to enhance the absorption of pharmacologically active agents through the stratum corneum. Other compounds which have been used to enhance skin permeability include: decylmethylsulfoxide (C_{10}MSO); diethylene glycol monoethyl ether; polyethylene glycol monolaurate (PEGML; *see*, *e.g.*, U.S. Patent No. 4,568,343 to Leeper *et al.*); glycerol monolaurate (U.S. Patent No. 4,746,515 to Cheng *et al.*); propylene glycol monolaurate (*e.g.*, U.S. Patent No. 4,764,379 to Sanders *et al.*); ethanol (*e.g.*, as in U.S. Patent No. 4,379,454 to Campbell *et al.*); eucalyptol (U.S. Patent No. 4,440,777); lecithin (U.S. Patent No.

4,783,450); the 1-substituted azacycloheptan-2-ones, particularly 1-n-dodecylcyclazacycloheptan-2-one (available under the trademark Azone® from Nelson Research & Development Co., Irvine, CA; see U.S. Patent Nos. 3,989,816, 4,316,893, 4,405,616 and 4,557,934); "cell envelope disordering compounds" such as methyl laurate or oleic acid in combination with N-(hydroxyethyl) pyrrolidone (U.S. Patent No. 4,537,776 to Cooper) C_3-C_4 diols (U.S. Patent No. 4,552,872 to Cooper *et al.*, European Patent Application Publication No. 043738); or a binary system of oleic acid, oleins or oleyl alcohol in combination with a lower alcohol (U.S. Patent No. 4,863,970 to Chang *et al.*).

References which relate to lower aliphatic esters of lower aliphatic carboxylic acids or lower alkanols: European Patent Publication No. 261429, which describes the use of propylene glycol in combination with a fatty acid such as linoleic acid; U.S. Patent No. 4,573,996 to Kwiatek *et al.*, which describes the use of glycols in transdermal formulations; and U.S. Patent No. 4,781,926 to Hyon *et al.*, which describes transdermal formulations containing either ethyl acetate or propylene glycol as a permeation enhancer.

References which relate to drug-specific transdermal systems: U.S. Patent No. 4,752,478 to Bondi *et al.* and U.S. Patent No. 4,938,759 to Enscore *et al.* describe systems for the transdermal administration of timolol base; U.S. Patent Nos. 4,560,553 to Zupan, 4,440,777 to Zupan, and 4,990,340 to Hidaka all describe pharmaceutical preparations formulated with timolol maleate. PCT published Patent Application No. WO88/09676 and U.S. Patent No. 4,806,341 to Chien *et al.* relate to the transdermal administration of buprenorphine, while U.S. Patent No. 4,573,995 to Chen *et al.* describes a system for the transdermal administration of nalbuphine.

Transdermal systems containing rate-controlling membranes: U.S. Patent No. 4,615,699 to Gale *et al.* describes a transdermal therapeutic system for the administration of nitroglycerin, which contains a rate-controlling membrane of ethylene-vinyl acetate. U.S. Patent Nos. 3,731,683, 3,854,480, and 3,996,934 to Zaffaroni describe a transdermal drug delivery device containing a wall member which is stated to meter the flow of drug. U.S. Patent No. 4,262,003 to Urquhart *et al.* describes a transdermal therapeutic system for administering scopolamine base, wherein the system contains a membrane for controlling the rate at which drug is released from the drug reservoir. U.S. Patent No. 4,834,979 to Gale describes a medical bandage for administering drug to the skin; the device contains a polymeric membrane apparently designed to control the rate of drug release from the drug reservoir.

Summary of the Invention

Accordingly, it is a primary object of the invention to address the above-mentioned need in the art by providing a transdermal drug delivery device containing a rate-controlling means effective to control drug flux but which does not limit the flow of enhancer from the device.

It is another object of the invention to provide such a device in which the rate-controlling means is a polymeric membrane.

It is still another object of the invention to provide such a device in which the polymeric membrane is an ethylene-vinyl acetate based membrane.

It is yet another object of the invention to provide such a device containing a skin permeation enhancer composition of a lower aliphatic ester of a lower aliphatic carboxylic acid in combination with a lower alkanol, and optionally additional permeation enhancing components such as a lower aliphatic ester of a higher carboxylic acid.

It is a further object of the invention to provide such a device for the transdermal administration of captopril.

It is still a further object of the invention to provide such a device for the transdermal administration of timolol or a salt thereof.

It is yet a further object of the invention to provide such a device for the transdermal administration of buprenorphine.

It is yet a further object of the invention to provide such a device for the transdermal administration of nalbuphine.

It is another object of the invention to provide a method for administering a drug transdermally using the aforementioned drug delivery system.

Additional objects, advantages, and novel features of the invention will be apparent to those skilled in the art upon a review of the Detailed Description and Examples which follow.

In a first aspect of the invention, then, a transdermal drug delivery device is provided for administering a pharmacologically active agent through a selected area of skin over a sustained time period, comprising a laminated composite of:

(a) a backing layer which is substantially impermeable to the pharmacologically active agent and which defines the upper surface of the device during use;

(b) laminated thereto, a reservoir layer containing a therapeutically effective amount of the pharmacologically active agent and a permeation enhancer composition comprising (i) a lower aliphatic ester of a lower aliphatic carboxylic acid, and (ii) a lower alkanol;

(c) a release rate-controlling means which controls the flow of pharmacologically active agent but not the flow of permeation enhancer composition from the device; and

(d) means for maintaining the device in agent-and enhancer-transmitting relationship to the skin.

In another aspect of the invention, a method is provided for administering a pharmacologically active agent transdermally, which comprises applying the above-defined laminated composite to a selected area of intact skin for a time period effective to produce the desired therapeutic effect.

Brief Description of the Figures

Figure 1 is a sectional representation of a preferred transdermal patch which may be used in conjunction with the methods and compositions of the invention.

Figure 2 graphically illustrates the flux of captopril into an infinite reservoir permeating through human skin, as described in Example 1.

Figure 3 graphically illustrates the flux of propylene glycol into an infinite reservoir from a transdermal patch (Figure 3A) and the cumulative delivery of propylene glycol from the patch over a 24 hour period (Figure 3B), as described in Example 2.

Figure 4 graphically illustrates the flux of ethyl acetate into an infinite reservoir from a transdermal patch and the cumulative delivery of ethyl acetate from the patch over a 24 hour period, as described in Example 2.

Figure 5 graphically illustrates the flux of ethyl acetate into an infinite reservoir from a transdermal patch, with and without skin, over a 24 hour period, as described in Example 3.

Figure 6 graphically illustrates the flux of captopril into an infinite reservoir from a transdermal patch over a 24 hour period, as described in Example 4.

Figure 7 graphically illustrates the flux of captopril into an infinite reservoir permeating through skin or from a transdermal patch permeating through skin over a 60 hour period, as described in Example 5.

Figures 8A and 8B graphically illustrate the flux of ethyl acetate and ethanol, respectively, into an infinite reservoir permeating from a transdermal patch loaded with variable permeation enhancer vehicle compositions and captopril through human cadaver abdominal skin over a 24 hour period, as described in Example 6.

Figures 9A and 9B graphically illustrate the flux of captopril into an infinite reservoir permeating from a transdermal patch loaded with variable permeation enhancer vehicle compositions and captopril through human cadaver abdomen and thigh skin, respectively, over a 24 hour period, as described in Example 7.

Figure 10 graphically illustrates the flux of timolol maleate through skin, through an ethylene-vinyl acetate membrane, and through an ethylene-vinyl acetate membrane placed on skin, as described in Example 8.

Figures 11A and 11B graphically illustrate solvent flux versus time for the experiment of Example 8.

Detailed Description of the Invention

Before describing the present compositions, systems and methods of the invention in detail, it is to be understood that this invention is not limited to the particular drugs, transdermal devices, or laminate materials described herein, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an", and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to a laminated structure containing "a drug" includes a mixture of two or more drugs, reference to "a lower aliphatic ester" includes reference to one or more of such esters, reference to "a lower alkanol" includes reference to one or more lower alkanols, and the like.

In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

"Penetration enhancement" or "permeation enhancement" as used herein relates to an increase in the permeability of skin to a pharmacologically active agent, *i.e.*, so as to increase the rate at which the agent permeates into and through the skin. A "permeation enhancer" is a material which achieves such permeation enhancement, and a "penetration enhancing amount" of an enhancer as used herein means an amount effective to enhance skin penetration of a selected agent to a desired degree, *i.e.*, to effect the desired pharmacologic response.

By "transdermal" drug delivery, applicant is using the term in its conventional sense, *i.e.*, to indicate delivery of a drug by passage through the skin and into the blood stream. By "transmucosal" drug delivery, applicant intends delivery of a drug by passage of a drug through the mucosal tissue into the blood stream. "Topical" drug delivery is used to mean local administration of a topical drug as in, for example, the treatment of various skin disorders. Aspects of the invention which are described in the context of "transdermal" drug delivery, unless otherwise specified, can apply to transmucosal or topical delivery as well. That is, the compositions, systems, and methods of the invention, unless explicitly stated otherwise, should be presumed to be equally applicable with any one of these three modes of drug delivery.

The term "drug" or "pharmacologically active agent" as used herein is intended to mean a compound or composition of matter which, when administered to an organism (human or animal) induces a desired pharmacologic and/or physiologic effect by local and/or systemic action. In general, the terms include the therapeutic or prophylactic agents in all major therapeutic or prophylactic areas of medicine. Examples of drugs useful in conjunction with the present invention include: anti-infectives such as antibiotics and antiviral agents; analgesics and analgesic combinations; anorexics; antihelminthics; antiarthritics; antiasthmatic agents; anticholinergic agents; anticonvulsants; antidepressants; antidiabetic agents; antidiarrheals; antihistamines; anti-inflammatory agents; antimigraine preparations; anti-motion sickness drugs; antinauseants; antineoplastics; antiparkinsonism drugs; antipruritics; antipsychotics; antipyretics; antispasmodics; anticholinergics; sympathomimetics; xanthine derivatives; cardiovascular preparations including calcium channel blockers and beta-blockers such as pindolol and antiarrhythmics; antihypertensives; diuretics; vasodilators including general coronary, peripheral and cerebral; central nervous system stimulants; cough and cold preparations, including decongestants; steroids; hypnotics; immunosuppressives; muscle relaxants; parasympatholytics; psychostimulants; sedatives; and tranquilizers. For purposes of the aforementioned definition, "drugs" as used herein also include locally administered topical medicaments such as antibacterial agents, antifungals, antimicrobials, cutaneous growth enhancers, antipsoriatics, anti-acne medicaments, and the like.

"Carriers" or "vehicles" as used herein refer to carrier materials without pharmacological activity which are suitable for administration in conjunction with the presently disclosed and claimed compositions, and include any such carrier or vehicle materials known in the art, *e.g.*, any liquid, gel, solvent, liquid diluent, solubilizer, or the like. The carriers and vehicles suitable herein

are "pharmaceutically acceptable" in that they are nontoxic, do not interfere with drug delivery, and are not for any other reasons biologically or otherwise undesirable. Examples of specific suitable carriers and vehicles for use herein include water, mineral oil, silicone, inorganic gels, aqueous emulsions, liquid sugars, waxes, petroleum jelly, and a variety of other oils and polymeric materials.

By a "therapeutically effective" amount of a drug or pharmacologically active agent is meant a nontoxic but sufficient amount of the drug or agent to provide the desired therapeutic effect.

The invention is thus, in one embodiment, a transdermal drug delivery device which comprises a laminated composite of a backing layer, a drug reservoir layer, a release rate-controlling means, and a means for maintaining the device in agent- and enhancer-transmitting relationship to the skin. The device may also include one or more other layers, *e.g.*, additional drug and/or enhancer reservoirs or the like.

In these composites, the backing layer will function as the primary structural element of the device and provide the device with much of its flexibility. This layer also serves as a protective covering to prevent loss of drug and enhancer via transmission through the upper surface of the device. The backing layer may also be used to impart the device with a desirable or necessary degree of occlusivity which in turn causes the area of skin on which the device is placed to become hydrated. The backing is preferably made of a sheet or film of a flexible elastomeric material, and may or may not be metallized. Suitable flexible elastomeric materials include polyether block amide copolymers, polyurethanes, silicone elastomers, rubber-based polyisobutylene, styrene, polyethylene, polypropylene, polyesters, or the like. The preferred polymer used for the backing will depend primarily on the particular pharmacologically active agent incorporated into the device.

The reservoir layer which contains the selected pharmacologically active agent in a therapeutically effective amount and the skin permeation enhancer composition may comprise either an adhesive polymer or a gelled system, which is preferably but not necessarily of a material in which the selected drug or vehicle has moderate solubility and diffusivity. Examples of suitable adhesive materials which may be used to formulate the drug reservoir layer include polysiloxanes, polyacrylates, polyurethanes, polyisobutylene, and tacky rubbers. It is preferred, however, that the drug reservoir be a gelled system; either aqueous or nonaqueous gelled systems may be used. An exemplary gelled formulation will include about 0.1 to 40 wt.% drug and 1 to 10 wt.% gelling agent, with the remainder of the formulation being enhancer, carriers, or the like. It will be appreciated by those skilled in the art, however, that the relative quantities of drug, enhancer, carrier (if any), and gelling agent will vary, depending on a number of factors, including the particular drug to be administered, desired dosage, and the like. Optimization of the drug/enhancer reservoir composition may be carried out readily using routine methods known to those working in the field of transdermal drug delivery. Suitable gelling agents include, for example, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethylcellulose, carbopol resins, and the like.

The release rate-controlling means of the invention will typically be a polymeric membrane placed in the flow path of drug from the reservoir layer to the skin, although the drug reservoir

matrix itself may serve as a release rate-controlling element. The membrane material will generally be selected from the group consisting of ethylene-vinyl acetate (EVAc), ethylene-vinyl acetate organic acid terpolymer, polyamide, polyester, and acrylic resins. Preferably the release rate-controlling membrane has an vinyl acetate (VAc) content of at least about 15 wt.%, more preferably at least about 18 wt.%, most preferably at least about 25 wt.%.

Underlying or adjacent to the release rate-controlling membrane is a means for maintaining the device in agent- and enhancer-transmitting relationship to the skin. The means is typically an adhesive means formulated from an adhesive material which is chemically and physically compatible with all components of the device and which is pharmacologically acceptable, *i.e.*, it should be of a material suitable for placement on the skin. Such adhesive materials will typically be selected from that class of materials which may be used for the drug reservoir layer; preferred materials include polysiloxanes, polyacrylics, and polyisobutylene.

As noted above, the transdermal devices of the invention are formulated with an enhancer composition suitable for enhancing the rate of penetration of a selected drug through the skin, wherein the composition comprises a lower aliphatic ester of a lower aliphatic carboxylic acid and propylene glycol. As used herein, the term "lower" is used to mean a chemical compound having six carbon atoms or less. Preferred materials useful as the lower aliphatic esters have a total of from about three to about six carbon atoms in their esterifying groups plus their acid groups. Thus, typical materials include methyl butrate, methyl proprionate, methyl acetate, ethyl butrate, ethyl propionate, ethyl acetate, propyl butrate, propyl propionate, and propyl acetate. Among these materials, special preference is given to ethyl acetate.

The permeation enhancer compositions of the invention also contain a lower alkanol. The lower alkanol can be a monoalkanol such as methanol, ethanol, 1-propanol, 2-propanol, or a butanol (n-, i- or t-butanol), or it may be a diol such as propylene glycol. Propylene glycol and ethanol are particularly preferred.

The enhancers of the invention preferably contain on the order of 25 wt.% to 90 wt.% lower aliphatic ester and approximately 10 wt.% to 75 wt.% lower alkanol. However, the compositions may also include carriers or vehicles as described above, and/or various additional agents and ingredients such as fragrances, pacifiers, preservatives, antioxidants, gelling agents, perfumes, thickening agents, stabilizers, surfactants, emollients, coloring agents, and the like, so long as they are pharmaceutically acceptable and compatible with the selected pharmacologically active agent in the permeation enhancer composition as described above. Particularly preferred additives include hydrophobic co-solvents such as squalene, decylmethylsulfoxide, and isopropyl myristate, and surfactants, including anionic, cationic, nonionic, and amphoteric surfactants. If such co-solvents or surfactants are present, they will preferentially be included at less than about 15 wt.%, preferably less than about 10 wt.% of the total enhancer composition. Addition of a lower aliphatic ester of a higher carboxylic acid (*i.e.*, containing seven carbon atoms or more), such as isopropyl myristate, is particularly preferred.

While a variety of pharmacologically active agents may be administered using the compositions of the present invention, particularly preferred active agents are selected from the

group consisting captopril, timolol, nalbuphine, buprenorphine, and salts thereof. Captopril and timolol maleate are especially preferred.

For captopril, a preferred enhancer formulation contains about 25 wt.% to 90 wt.% lower aliphatic ester and about 10 wt.% to 75 wt.% lower alkanol. Particularly preferred enhancer compositions for use with captopril contain about 50 wt.% to 90 wt.% ethyl acetate, 25 wt.% to 45 wt.% propylene glycol, and 0 wt.% to 15 wt.%, preferably 5 wt.% to 10 wt.%, isopropyl myristate. More particularly preferred enhancer compositions for use with captopril contain 25 wt.% to 65 wt.% ethyl acetate and 35 wt.% to 75 wt.% ethanol. For timolol maleate, an optimum enhancer formulation contains about 70 wt.% to 90 wt.% lower aliphatic ester (preferably ethyl acetate) and about 10 wt.% to 30 wt.% lower alkanol (preferably propylene glycol or ethanol). The amount of drug contained within the composition will depend on a variety of factors, including the desired rate of delivery, the desired dosage, the disease to be treated, the nature and activity of the drug, the desired effect, possible adverse reactions, the ability and speed of the drug selected to reach its intended target, and other factors within the particular knowledge of the patient and physician.

Prior to use, the laminated composite also includes a release liner layer. Just prior to use, this layer is removed from the device to expose the basal surface of the device. The release liner will normally be made from a drug/enhancer-impermeable material that is inherently "strippable" or rendered so by techniques such as silicone or fluorocarbon treatment.

An exemplary system is illustrated in cross-section in Figure 1. In the figure, the transdermal patch is shown generally at **10**, with backing material **14** overlying drug reservoir **12**. Adjacent to and underlying the reservoir is a release rate-controlling membrane **16** which, as mentioned above, is preferably comprised of a vinyl acetate-containing material. Underlying membrane **16** is a protective layer **18** which is typically comprised of a material similar to that selected for backing **14**. Release liner **20** forms the basal surface of the device prior to use, and may be peeled away to expose adhesive ring **22**. Heat seals **24, 26, 28**, and **30** ensure that the various components and layers of the device remain bonded together.

Preferred daily dosages obtained with the present methods and systems will, similarly, vary with the drug administered. The targeted daily dosage will depend on the individual being treated, the indication addressed, the length of time the individual has been on the drug, and the like.

The following examples are put forth so as to provide those with ordinary skill in the art with a complete disclosure and description of how to formulate compositions and systems of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (*e.g.*, amounts, temperatures, etc.), but some experimental errors and deviations should be allowed for. Unless indicated otherwise, temperatures are in degrees Centigrade, and pressure is at or near atmospheric.

Specific Embodiments

Skin Permeability Studies, Methods and Materials: A system employing nine glass Franz diffusion cells was used for the permeability experiments. The cells were modified with inlet and outlet receiver ports to allow continuous flow through the cells. The human cadaver skin used in the experiments was excised from the abdomen, back or thigh area of 40- to 80-year-olds within 12 hours post-mortem at a thickness ranging from 150-600 µm. The skin was stored frozen. The skin was then thawed, cut to circular pieces of approximately 2.0-5.0 cm^2, and placed on the cells, epidermis side up, to equilibrate for one hour, with a glass cell cap clamped above.

The surface area exposed to the donor phase was 0.65 cm^2 or 2.0 cm^2. The donor vehicles were prepared by saturating the drug to be tested in the different enhancer mixtures to ensure a constant driving force. In some experiments, donor vehicles were prepared using other concentrations of drugs. Captopril was saturated at 33 wt.%. Timolol maleate was saturated at 25 wt.%. The suspensions were stirred overnight. In some experiments, donor vehicles were prepared using other concentrations of drugs. At the start of the experiment, 325 µl of the saturated mixture was pipetted through the cell cap directly onto the skin, and the cap sealed with a glass stopper. In some experiments, the donor vehicle was gelled by the addition of a combination of hydroxypropyl cellulose and Carbopol 1342 (obtained from B.F. Goodrich, Cleveland, Ohio) at a concentration of 1 to 2 wt.% (and added to the skin at a concentration of 150 µL/cm^2). In other experiments, entire transdermal devices were placed on the skin or in the cell without skin.

The receptor phase, in contact with the underside of the skin, was phosphate-buffered (0.01 M, pH 7.4) isotonic saline with 0.05% sodium azide added to prevent bacterial growth. The cells were maintained at 37°C by circulating thermostatically controlled water through a jacket surrounding the cell body.

Receptor phase solution was pumped through the diffusion cells by means of a Manostat Cassette Pump drive unit. A fraction collector was used to collect the cell effluent. The flow rate was set so that drug concentration in the receptor phase remained well below saturation; a typical flow rate was 5 ml/hr. Uniform mixing of the drug in the receptor phase was achieved by a small magnetic stirring bar driven by an external 600 rpm motor. Fractions were collected at regular intervals and analyzed for the selected drug using HPLC. Each donor vehicle/therapeutic agent formulation was tested in triplicate and the 24-hour cumulative drug deliveries averaged for the three cells.

Example 1

(a.) Skin Permeability Studies: Captopril

The above procedures were used to evaluate the flux of captopril through human skin, an EVAc membrane (Elvax 250, obtained from DuPont) or an EVAc/skin combination. To prevent formation of a disulfide of captopril, 0.001 M citric acid as an antioxidant and 0.001 M ethylenediaminetetraacetic acid (EDTA) were added to the receptor phase solution.

Captopril concentration in the receptor phase was measured using HPLC. No sample pretreatment was required. The HPLC analyses were performed on a Waters 840 system consisting of two Model 510 pumps, a Model 481 UV detector, a Model 710 B WISP (sample processor), and a Digital Computer Model 350 microprocessor/programmer. The column used was a 4.6 mm x 25 cm Whatman ODS-3 Partisil C-18 at 40°C. Captopril was measured using a mobile phase of 0.10 M phosphate buffer, pH 3.0: acetonitrile, at a flow rate of 1.0 ml/min. After an initial 2 min. at 0% acetonitrile, the acetonitrile content was raised to 15% for captopril elution. The acetonitrile portion was lowered to 0% for the next injection. Run time was 19 minutes. Absorbance monitoring was at 240 nm, and the retention time found to be 14.0 min.

The goal of this experimentation was to evaluate the flux of captopril from a saturated solution in an ethyl acetate (EtAc)/propylene glycol (PG)/isopropyl myristate (IPM) (0.55:0.40:0.05) donor vehicle through human thigh skin. A minimum target flux of 60 $\mu g/cm^2/hr$ was calculated, for a 25 cm^2 patch. This flux corresponds to a cumulative delivery of 2.0 mg/cm^2. The experimental results are summarized in Figure 2. The flux of captopril through human skin never reached a steady-state condition over the 24-hour testing period.

(b.) Preparation of Transdermal Patches

Transdermal patches were prepared as follows. A 300 µL reservoir was created in the backing material (Scotchpak #1009, Health Care Specialties Division, 3M) using a steel mold machined at SRI International, Menlo Park, CA. The steel mold consisted of three parts: 1/2" (1.27 cm) thick by 3" (7.62) i.d. upper and lower cylindrical pieces and a 3/4" (1.91 cm) long plunger. The lower half of the mold had a depression that was used to shape the reservoir in the backing material. The upper half of the mold had a 2.0 cm^2 hole drilled through it to accommodate the third part of the mold, the plunger. The bottom of the plunger was machined to fit into the depression in the lower half of the mold. The depression was defined by a 2.0 cm^2 circular area cut about 1 mm into the lower half of the mold. The edges of the depression were rounded, and there was a 6 mil clearance between the sides of the depression and the plunger, to prevent shearing of the backing material.

The reservoir was created by centering a 1.75" (4.45 cm) i.d. piece of backing material on the lower half of the mold, with the aluminized side up. The upper half of the mold was secured to the lower half using allen screws, immobilizing the backing material. The plunger was pushed through the hole in the upper half of the mold until it rested on the backing material. The entire mold was then placed in a heat press at 185°F (85°C) for fifteen minutes. The upper and lower plates of the heat press were then brought together until the backing layer was driven to the bottom of the depression in the lower half of the mold. The pressure used was less than about 500 psi

(3447 kPa). After fifteen minutes at 185°F (85°C), the heat press plates were moved apart, and the mold was removed and placed in a second press that was at room temperature. The plates of this press were brought together as before and the mold allowed to cool with the plunger at the bottom of the depression. The backing material with reservoir was then rinsed in 70% isopropanol and allowed to dry.

After the reservoir was formed in the backing layer, a ring of transfer adhesive (3M Pharmaceutical Grade Transfer Adhesive No. 9871) with a paper release liner (3M Silicone Treated Paper Release Liner No. 9743) was added. The adhesive ring was prepared as follows. First, the non-sticking layer was removed from a portion of the transfer adhesive and a piece of the paper release liner added. 1.25" (3.18 cm) i.d. circles were punched out of the transfer adhesive/paper release liner laminate. Then, 1.75" (4.45 cm) i.d. circles were punched out. The result was a ring with a 1.75" (4.45 cm) outer diameter and a 1.25" (3.18 cm) inner diameter. The paper release liner was removed and the adhesive attached to the backing layer. The outer layer of material was removed from the adhesive ring, exposing the adhesive. The paper release liner (previously removed) was then placed on the adhesive. When the paper release liner is removed, the adhesive on the backing layer can be affixed to the skin.

A captopril patch was then prepared as follows: 300 µL donor solution (*e.g.*, EtAc/PG/IPM, 65:30:5 with 25 wt.% captopril, gelled using 1 wt.% hydroxypropyl cellulose) was pipetted into the reservoir using an SMI pipet. A 7/8"(2.22 cm) circular piece of 3 mil 18% EVAc membrane (3M) was heat-sealed over the top of the reservoir using a 1.8 cm i.d. heat sealer for 6 seconds at 133°C. The release liner was attached to the backing material using a 2.6 cm i.d. heat sealer for two seconds at 125°C.

<u>Example 2</u>

The above procedure was used to load transdermal patches with EtAc/PG/IPM (0.65/0.35/0.05) enhancer vehicle with 33 wt.% captopril. The captopril-containing vehicle was gelled with 1-2 wt.% hydroxypropyl cellulose and added to the skin at 150 µL/cm^2. Flux of PG and EtAc from the loaded transdermal patches into the receptor solution were evaluated as in Example 1.

EtAc and PG were measured using a Waters Fast Fruit Juice Column (7.8 mm x 15 cm). The mobile phase was 0.05% H_3PO_4 in water (vol/vol) at a flow rate of 1.5 ml/min. EtAc and PG were detected with a Waters Differential Refractometer Model 410.

The retention time of EtAc was 7.2 min while that of PG was 3.7 min. Standards of EtAc were collected alongside the sample fractions and used to correct for the loss of this volatile solvent prior to analysis by HPLC.

Cumulative PG and EtAc delivery from the transdermal patches into receptor solution was also evaluated. The experimental results are summarized in Figures 3 and 4, respectively.

The flux of PG reached a maximum of about 0.25 mg/cm^{2}hr after 4 hours and decreased progressively thereafter (Figure 3A). The cumulative PG delivered from the transdermal patch did not reach a steady-state condition for the 24 hour period of the experiment (Figure 3B).

In a qualitatively similar manner, the flux of EtAc reached a maximum of about 9 mg/cm^{2}hr after 4 hours and decreased progressively thereafter (Figure 4A). The cumulative EtAc delivered from the transdermal patch did not reach a steady-state condition for the 24 hour period of the experiment (Figure 4B).

Example 3

The procedures described in Example 2 were used to evaluate the flux of EtAc from transdermal patches, with and without human cadaver skin, and skin only. The experimental results are summarized in Figure 5.

As in Example 2, the flux of EtAc from the patch reached a peak of about 9.3 mg/cm^{2}hr at 4 hours. The flux of EtAc from the patch through skin reached a peak of about 3 mg/cm^2 at 6 hours and declined to a steady-state level thereafter. These results indicate that solvent delivery is controlled to a large extent by the skin.

Example 4

The procedures of Example 2 were used to evaluate the flux of captopril from transdermal patches into the receptor phase solution. The experimental results are summarized in Figure 6.

The captopril target flux was exceeded between 2 and 4 hours, and, unlike the permeability results observed using skin alone (see Example 1), a steady-state level of about 125 μg/cm^{2}hr was reached by 6 hours. This level was maintained for the 24 hour duration of the experiment.

Example 5

The procedures described in Example 2 were used to evaluate the flux of captopril into the receptor phase solution from transdermal patches through human back skin. Patches were left in place for 24 hours and either removed or removed and a second patch placed on the same skin. The procedures described in Example 1 were used to evaluate the flux of captopril from a gelled enhancer vehicle through skin only. The experimental results of both these procedures are summarized in Figure 7.

As previously described in Example 1, the flux of captopril from a gelled enhancer vehicle through skin into the receptor phase solution exceeded the target flux between 12 and 16 hours. Flux increased to a level of about 400 μg/cm^{2}hr by 32 hours and decreased thereafter until 50 hours when an apparently anomalous increase in flux was observed.

When the flux of captopril from a single transdermal patch through skin was evaluated target flux was again exceeded between 12 and 16 hours. A steady-state flux level of about 140 μg/cm^{2}hr was achieved by 24 hours and was maintained for an additional 8 hours despite the removal of the patch. The flux decreased thereafter until it dropped below the target level between 42 and 45 hours.

When the first patch was removed after 24 hours and replaced with a second patch on the same skin, the steady-state flux level increased slightly to about 200 μg/cm^{2}hr by 32 hours and

remained at that level for an additional 16 hours. The flux decreased thereafter to about 70 $\mu g/cm^2hr$ but did not drop below the target level for the remaining duration of the experiment.

Example 6

The procedure described in Example 1(b) was used to load transdermal patches made with 28 wt.% VAc-content EVAc copolymer membranes with various amounts of EtAc / ethanol (EtOH) (0.65:0.35, 0.50:0.50, 0.35:0.65) enhancer vehicle with 10 wt.% captopril. The captopril-containing vehicle was gelled and added to the skin as in Example 2. The procedures described in Example 2 were used to evaluate the flux of EtAc and EtOH from transdermal patches through human cadaver skin. The experimental results are summarized for EtAc and EtOH in Figures 8A and 8B, respectively.

The relationship between enhancer vehicle component flux and time was quantitatively similar to that seen in Example 2. The total amount of EtAc and EtOH delivered from the patches depended on the composition of the enhancer vehicle.

Example 7

The procedure described in Example 1(b) was used to load transdermal patches made with 28 wt.% VAc-content EVAc copolymer membranes with various amounts of EtAc / ethanol (EtOH) (0.65:0.35, 0.50:0.50, 0.35:0.65, 0.25:0.75, 0.15:0.85) enhancer vehicle with 10% captopril. The captopril-containing vehicle was gelled and added to the skin as in Example 2. The procedures described in Example 1(a) were used to evaluate the effect of enhancer vehicle composition on the flux of captopril from transdermal patches through human cadaver skin. The experimental results are summarized in Figures 9A (abdominal skin) and 9B (thigh skin).

The captopril target flux was exceeded when the enhancer vehicle composition (EtAc / EtOH) was 0.25:0.75, 0.35:0.65, 0.50:0.50 or 0.65:0.35. The longer lag time observed in the experiments depicted in Figure 9B is postulated to be due to the fact that the skin used was considerably thicker than in other experiments.

Example 8

The procedures of Example 1 were used to evaluate the flux of timolol maleate through human skin, through an EVAc membrane, and through an EVAc membrane placed on human skin.

Timolol concentration in the receptor phase was measured using HPLC. No sample pretreatment was required. The HPLC analyses were performed on a Waters 840 system consisting of two Model 510 pumps, a Model 481 UC detector, a Model 710 B WISP (sample/processor), and a Digital Computer Model 350 microprocessor/programmer. The column used wa a 4.6 mm x 25 cm Whatman ODS-3 Partisil C-18. Timolol was measured using a mobile phase of 0.05 M sodium acetate buffer, pH 3.5/90% acetonitrile (10% acetate buffer) (30/70) at a flow rate of 1.8 ml/min. Absorbance monitoring was performed at 295 nm, and the retention time was found to be 5.3 minutes.

The goal of this experiment was to evaluate the flux of timolol maleate, ethyl acetate and propylene glycol from a saturated drug solution in an ethyl acetate (EtAc) / propylene glycol (PG) / isopropyl myristate (IPM) (0.55:0.40:0.05) donor vehicle through human skin, through a 2 mil (28% vinyl acetate) EVAc membrane (3M), and through the membrane placed on the skin.

It was intended that the membrane be rate-controlling for the drug only, and yield a sustained flux for timolol at or near the minimum target flux of 5 μg/cm^2, which was calculated based on theoretical delivery from a 30 cm^2 patch.

The experimental results for timolol maleate are summarized in Figure 10. As can be seen, the membrane and membrane-skin composite yielded a much lower, controlled flux for timolol compared to timolol flux through skin. Using a thinner grade of the same type of membrane should result in a slightly higher, but similar release profile for timolol.

Ethyl acetate and propylene glycol concentration in the receptor phase was also measured, using the method outlined in Example 2. The experimental results for ethyl acetate and propylene glycol are summarized in Figures 11A and 11B, respectively. As can be seen, solvent flux was much higher through skin than through the membrane or membrane/skin composite, until the solvent neared depletion, at which point the solvent flux dropped toward zero.

WHAT IS CLAIMED IS:

1. A transdermal drug delivery device for administering a pharmacologically active agent through a selected area of skin over a sustained time period, comprising a laminated composite of:

(a) a backing layer which is substantially impermeable to the pharmacologically active agent and which defines the upper surface of the device during use;

(b) laminated thereto, a reservoir layer containing a therapeutically effective amount of the pharmacologically active agent and a permeation enhancer composition comprising (i) a lower aliphatic ester of a lower aliphatic carboxylic acid and (ii) a lower alkanol;

(c) a release rate-controlling means which controls the flow of pharmacologically active agent but not the flow of permeation enhancer composition from the device; and

(d) means for maintaining the device in agent- and enhancer-transmitting relationship to the skin.

2. The device of claim 1, wherein the enhancer composition comprises approximately 25 wt.% to 90 wt.% of the lower aliphatic ester of the lower aliphatic carboxylic acid and approximately 10 wt.% to 75 wt.% lower alkanol.

3. The device of claim 1, wherein the lower aliphatic ester of the lower aliphatic carboxylic acid is methyl butrate, methyl proprionate, methyl acetate, ethyl butrate, ethyl proprionate, ethyl acetate, propyl butrate, propyl proprionate, or propyl acetate, and the lower alkanol is methanol, ethanol, 1-propanol, 2-propanol, n-butanol, i-butanol, t-butanol, propylene glycol, ethylene glycol, or glycerin.

4. The device of claim 3, wherein the lower aliphatic ester of the lower aliphatic carboxylic acid is ethyl acetate and the lower alkanol is propylene glycol.

5. The device of claim 1, wherein the permeation enhancer composition additionally comprises (iii) a lower aliphatic ester of a higher aliphatic carboxylic acid.

6. The device of claim 5, wherein the lower aliphatic ester of the higher aliphatic carboxylic acid is isopropyl myristate.

7. The device of claim 1, wherein the release rate-controlling means comprises a membrane disposed in the flow path of the pharmacologically active agent from the reservoir layer to the skin.

8. The device of claim 7, wherein the membrane is comprised of a polymer of ethylene-vinyl acetate, ethylene vinyl acetate organic acid terpolymer, polyamide, polyester, or acrylic resins.

9. The device of claim 8, wherein the membrane is ethylene-vinyl acetate having a vinyl acetate content of at least about 15 wt.%.

10. The device of claim 1, wherein the reservoir layer is comprised of a gelled polymer.

11. The device of claim 1, wherein the pharmacologically active agent is a timolol, captopril, nalbuphine, buprenorphine, or salts thereof.

12. The device of claim 11, wherein the pharmacologically active agent is captopril.

13. The device of claim 7, wherein the means for maintaining the device in agent- and enhancer-transmitting relationship comprises a peripheral adhesive underlying the membrane.

14. A transdermal drug delivery device for administering captopril through the skin, comprising a laminated composite of:

(a) a backing layer which is substantially impermeable to captopril and which defines the upper surface of the device during use;

(b) laminated thereto, a reservoir layer of a gelled polymer containing a therapeutically effective amount of captopril and a permeation enhancer composition comprising ethyl acetate, propylene glycol and isopropyl myristate;

(c) a release rate-controlling means comprising a membrane disposed in the flow path of the captopril and the enhancer composition, and which controls the flow of captopril from the device; and

(d) means for maintaining the device in agent- and enhancer-transmitting relationship to the skin.

15. A method for administering a pharmacologically active agent transdermally, comprising applying to a selected area of intact skin a laminated composite of:

(a) a backing layer which is substantially impermeable to the pharmacologically active agent and which defines the upper surface of the device during use;

(b) laminated thereto, a reservoir layer containing a therapeutically effective amount of the pharmacologically active agent and a permeation enhancer composition comprising (i) a lower aliphatic ester of a lower aliphatic carboxylic acid and (ii) a lower alkanol;

(c) a release rate controlling means which controls the flow of pharmacologically active agent but not the flow of permeation enhancer composition from the device; and

(d) means for maintaining the device in agent- and enhancer-transmitting relationship with the skin.

16. The method of claim 15, wherein the enhancer composition comprises approximately 25 wt.% to 90 wt.% of the lower aliphatic ester of the lower aliphatic carboxylic acid and approximately 10 wt.% to 75 wt.% lower alkanol.

17. The method of claim 15, wherein the lower aliphatic ester is methyl butrate, methyl proprionate, methyl acetate, ethyl butrate, ethyl proprionate, ethyl acetate, propyl butrate, propyl proprionate, or propyl acetate, and the lower alkanol is methanol, ethanol, 1-propanol, 2-propanol, n-butanol, i-butanol, t-butanol, propylene glycol, ethylene glycol, or glycerin.

18. The method of claim 17, wherein the lower aliphatic ester is ethyl acetate and the lower alkanol is propylene glycol.

19. The method of claim 15, wherein the permeation enhancer composition additionally comprises (iii) a lower aliphatic ester of a higher aliphatic carboxylic acid.

20. The method of claim 19, wherein the lower aliphatic ester of the higher aliphatic carboxylic acid is isopropyl myristate.

21. The method of claim 16, wherein the release rate-controlling means comprises a membrane disposed in the flow path of the pharmacologically active agent from the reservoir layer to the skin.

22. The method of claim 16, wherein the membrane is comprised of a polymer of ethylene-vinyl acetate, ethylene vinyl acetate organic acid terpolymer, polyamide, polyester, or acrylic resins.

23. The method of claim 22, wherein the membrane is ethylene-vinyl acetate having a vinyl acetate content of at least about 15 wt.%.

24. The method of claim 16, wherein the reservoir layer is comprised of a gelled polymer.

25. The method of claim 16, wherein the pharmacologically active agent is timolol, captopril, nalbuphine, buprenorphine, or salts thereof.

26. The method of claim 25, wherein the pharmacologically active agent is captopril.

27. The method of claim 21, wherein the means for maintaining the device in agent- and enhancer-transmitting relationship comprises a peripheral adhesive underlying the membrane.

28. A method for administering captopril transdermally, comprising applying to a selected area of intact skin a laminated composite of:

(a) a backing layer which is substantially impermeable to captopril and which defines the upper surface of the device during use;

(b) laminated thereto, a reservoir layer of a gelled polymer containing a therapeutically effective amount of captopril and a permeation enhancer composition comprising ethyl acetate, propylene glycol, and isopropyl myristate;

(c) a release rate controlling means comprising a membrane disposed in the flow path of the captopril and the enhancer composition and which controls the flow of captopril from the device; and

(d) means for maintaining the device in agent-and enhancer-transmitting relationship with the skin.

29. A method for administering captopril transdermally, comprising applying to a selected area of intact skin a laminated composite of:

(a) a backing layer which is substantially impermeable to captopril and which defines the upper surface of the device during use;

(b) laminated thereto, a reservoir layer of a gelled polymer containing a therapeutically effective amount of captopril and a permeation enhancer composition comprising ethyl acetate and ethanol;

(c) a release rate controlling means comprising a membrane disposed in the flow path of the captopril and the enhancer composition and which controls the flow of captopril from the device; and

(d) means for maintaining the device in agent-and enhancer-transmitting relationship with the skin.

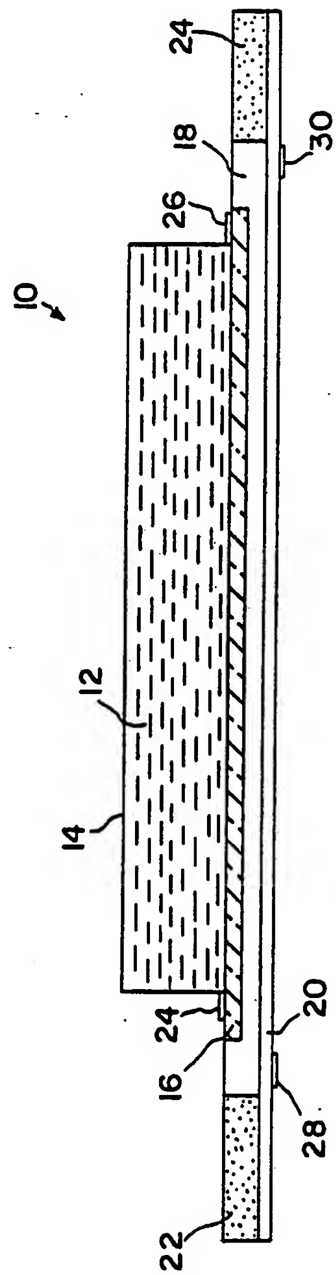

FIG.1

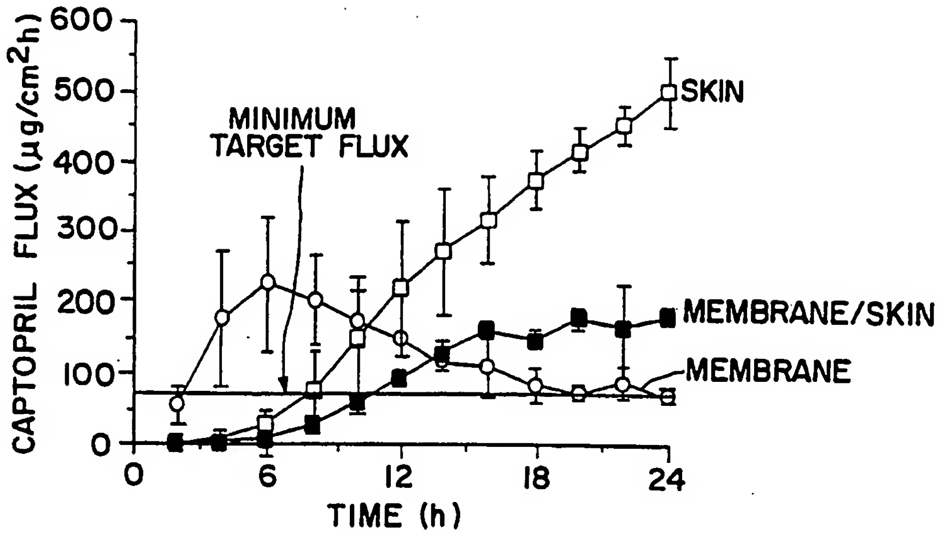

FIG.2

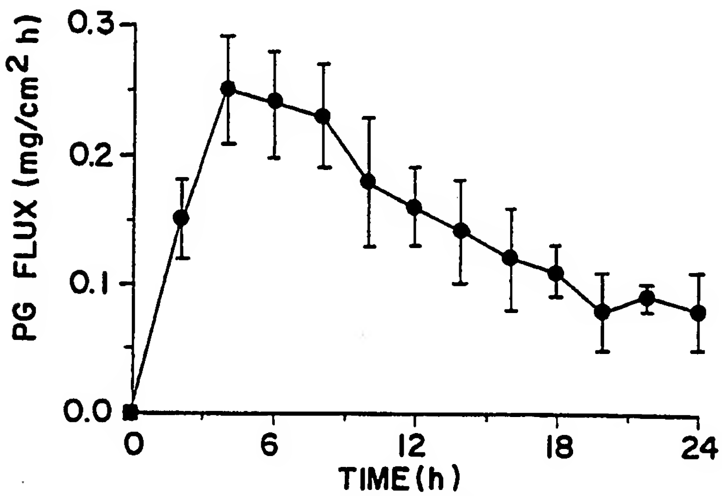

FIG.3A

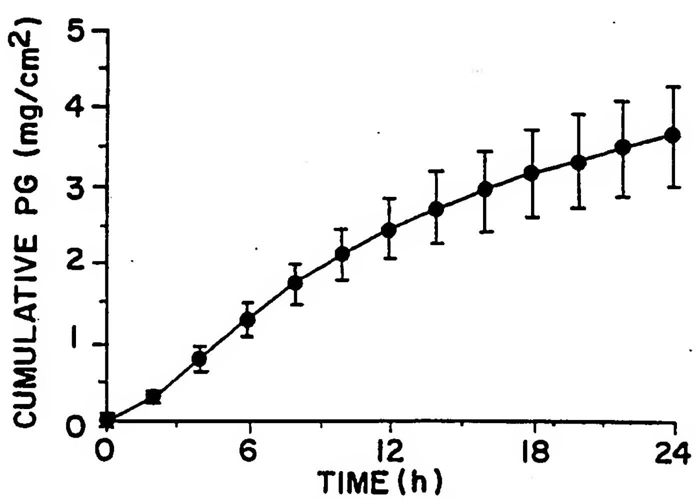

FIG.3B

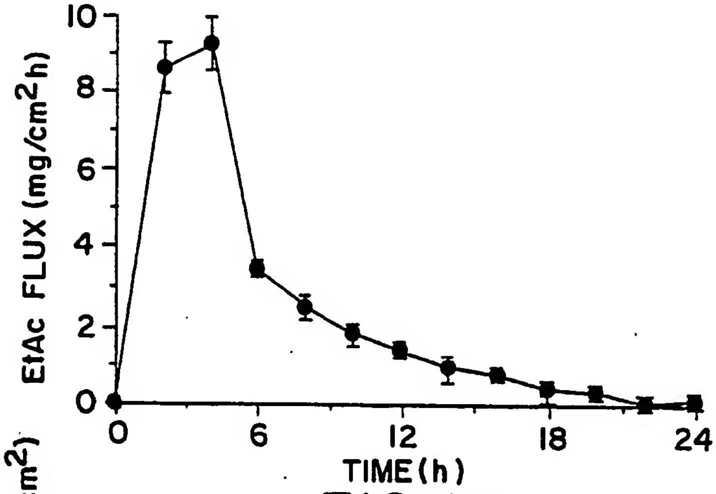

FIG.4A

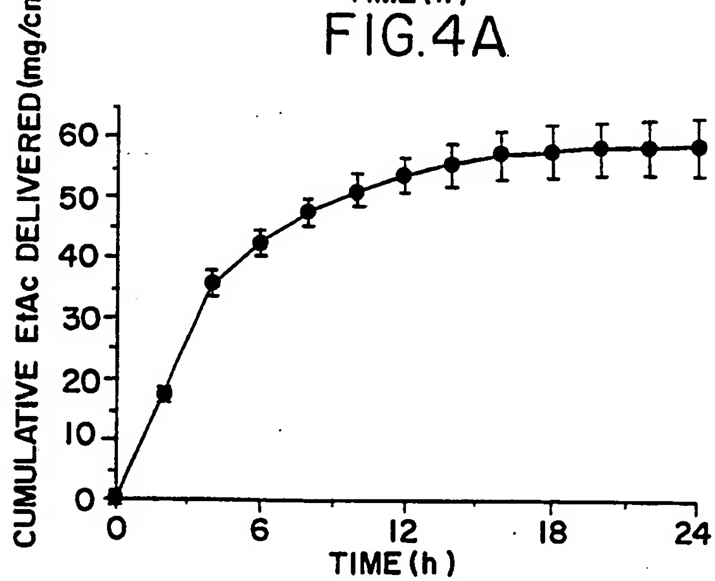

FIG.4B

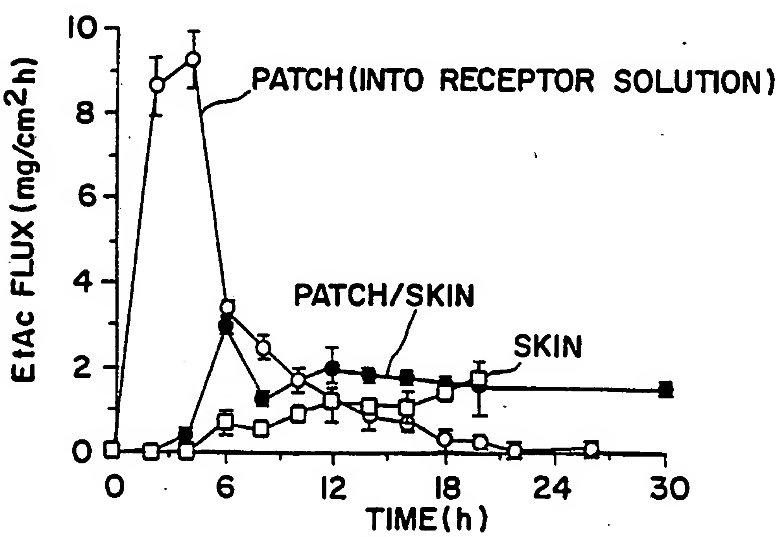

FIG.5

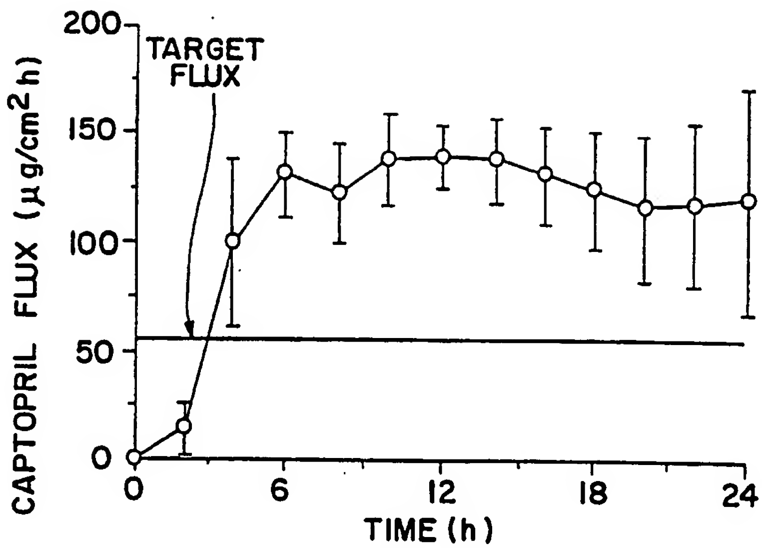
200
150
100
50
0
TARGET FLUX
CAPTOPRIL FLUX (μg/cm2 h)
0
6
12
18
24
TIME (h)

FIG.6

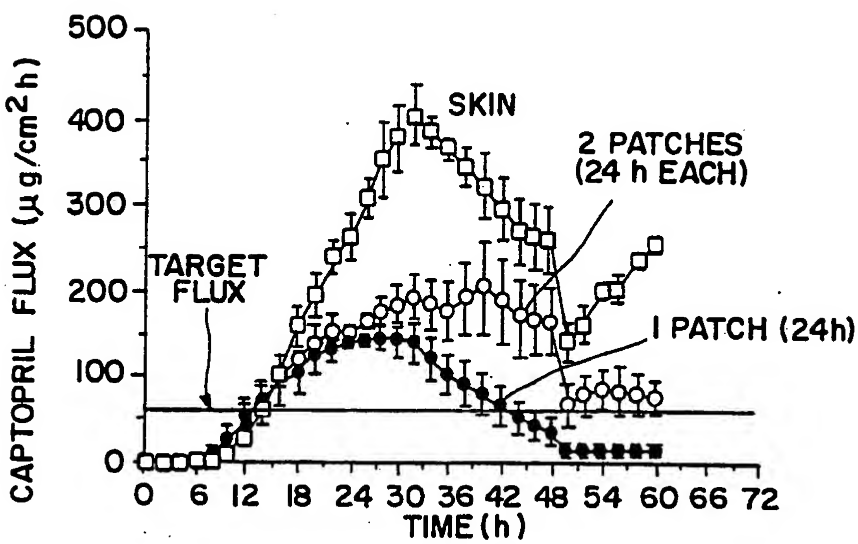
500
400
300
200
100
0
SKIN
2 PATCHES (24 h EACH)
TARGET FLUX
I PATCH (24h)
CAPTOPRIL FLUX (μg/cm2 h)
0 6 12 18 24 30 36 42 48 54 60 66 72
TIME (h)

FIG.7

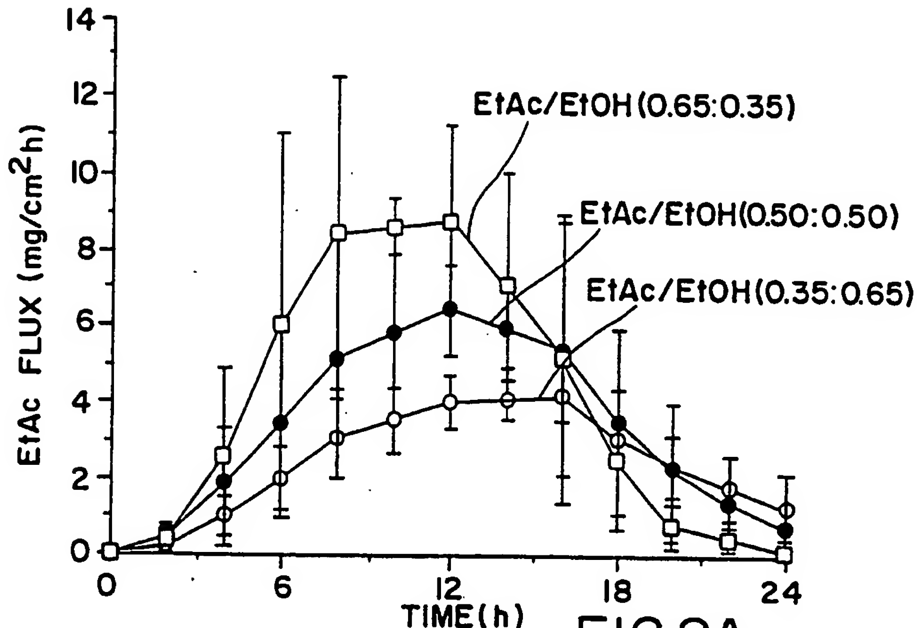
EtAc FLUX (mg/cm²h)
14
12
10
8
6
4
2
0
EtAc/EtOH(0.65:0.35)
EtAc/EtOH(0.50:0.50)
EtAc/EtOH(0.35:0.65)
0
6
12
18
24
TIME(h)

FIG.8A

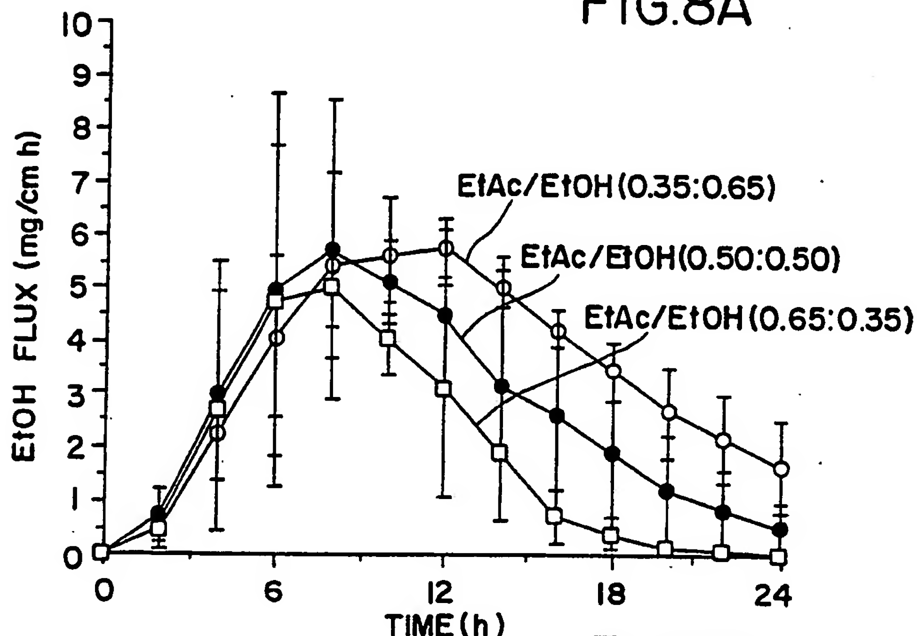
EtOH FLUX (mg/cm h)
10
9
8
7
6
5
4
3
2
1
0
EtAc/EtOH(0.35:0.65)
EtAc/EtOH(0.50:0.50)
EtAc/EtOH(0.65:0.35)
0
6
12
18
24
TIME(h)

FIG.8B

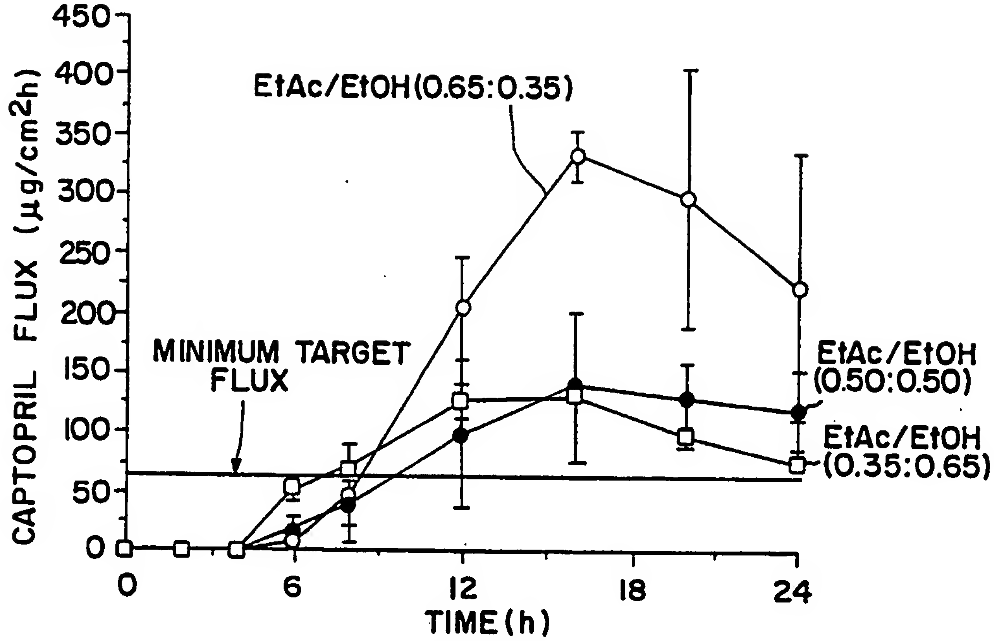
450
400
350
300
250
200
150
100
50
0
CAPTOPRIL FLUX (μg/cm^{2}h)
EtAc/EtOH(0.65:0.35)
MINIMUM TARGET FLUX
EtAc/EtOH (0.50:0.50)
EtAc/EtOH (0.35:0.65)
0
6
12
18
24
TIME (h)

FIG.9A

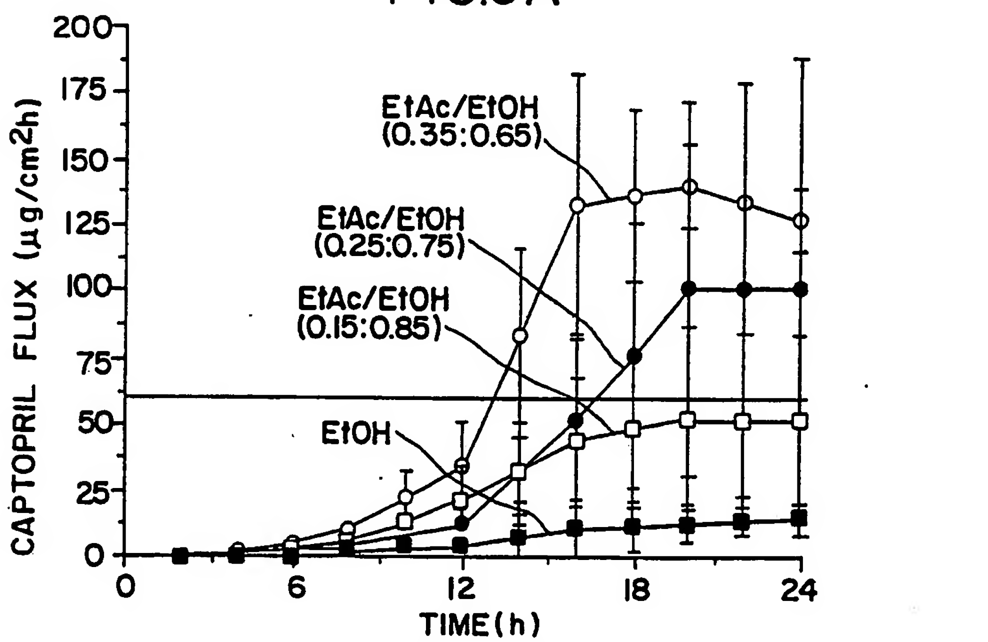
200
175
150
125
100
75
50
25
0
CAPTOPRIL FLUX (μg/cm^{2}h)
EtAc/EtOH (0.35:0.65)
EtAc/EtOH (0.25:0.75)
EtAc/EtOH (0.15:0.85)
EtOH
0
6
12
18
24
TIME (h)

FIG.9B

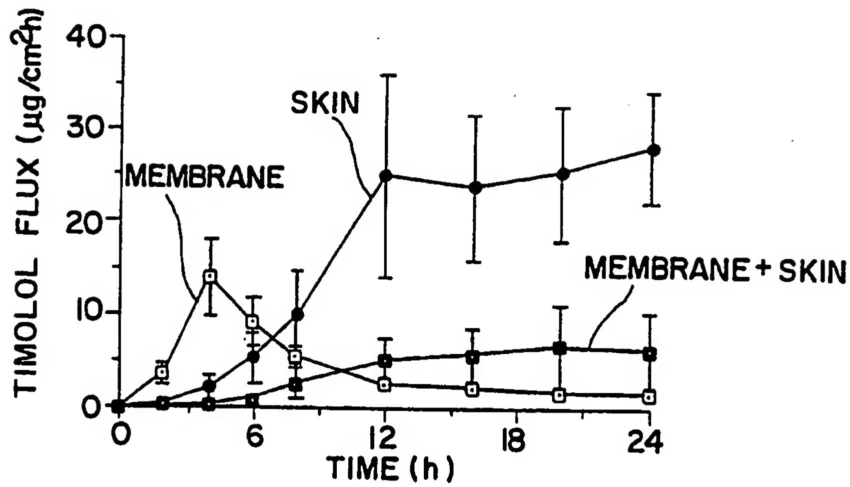

FIG. 10

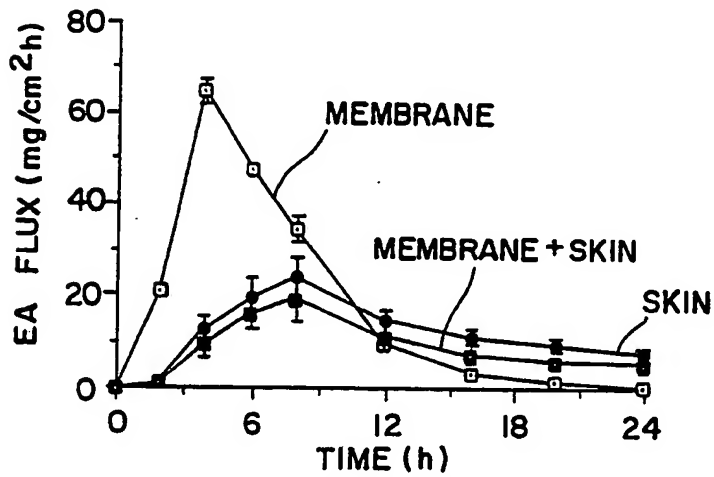

FIG. 11A

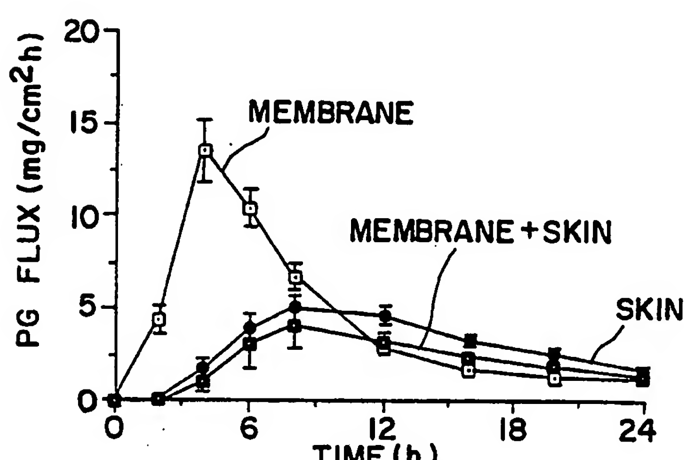

FIG. 11B

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 93/04442

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K9/70; A61K47/14; A61K47/10

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	JJOURNAL OF PHARMACEUTICAL SCIENCES vol. 78, no. 6, June 1989, pages 477 - 480 FRIEND D.R. ET AL 'TRANSDERMAL DELIVERY OF LEVONORGESTREL IV : EVALUATION OF MEMBRANES'	1-3, 7-10,13, 15-17, 21-24,27
Y	see the whole document	4-6,11, 12,14, 18-20, 26,28,29

A	BURI P. ET AL 'FORMES PHARMACEUTIQUES NOUVELLES' 1985 , TEC & DOC LAVOISIER , PARIS see page 392	1

	-/--	

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

1

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
17 AUGUST 1993	31. 08. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	BOULOIS D.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category°	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
E	WO,A,9 308 841 (SRI INTERNATIONAL) 13 May 1993 see page 11, line 22 - page 12, line 31 see page 17 - page 20; examples 2,3 see claims	1-29
Y	DATABASE WPI Section Ch, Week 9038, Derwent Publications Ltd., London, GB; Class A12, AN 90-287110 & JP,A,2 202 813 (SEKISUI CHEM IND KK) 10 August 1990 see abstract	12,14, 26,28,29
Y	WO,A,9 205 811 (ETHICAL PHARMACEUTICALS LIMITED) 16 April 1992 see page 9, line 26 - page 11, line 32 see page 13 - page 14; example 2 see page 15 - page 16; example 5 see figures 1,2	11
Y	EP,A,0 399 432 (TAKEDA CHEMICAL INDUSTRIES LTD) 28 November 1990 see page 6 - page 7; example 2	4-6,14, 18-20,28
Y	EP,A,0 368 406 (NORWICH EATON PHARMACEUTICALS INC) 16 May 1990 see page 5 - page 6; example 1	11
Y	EP,A,0 452 837 (NITTO ELECTRICAL INDUSTRIAL CO LTD) 23 October 1991 see page 11; examples 4,6	11
A	JOURNAL OF CONTROLLED RELEASE vol. 9, no. 1, 1989, AMSTERDAM pages 33 - 41 FRIEND D. ET AL 'SIMPLE ALKYL ESTERS AS SKIN PERMEATION ENHANCERS' see the whole document	1

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9304442
SA 73881

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 17/08/93
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9308841	13-05-93	None		
WO-A-9205811	16-04-92	AU-A-	8629591	28-04-92
		CA-A-	2093321	06-04-92
		EP-A-	0551349	21-07-93
		GB-A-	2249956	27-05-92
EP-A-0399432	28-11-90	CA-A-	2017442	25-11-90
		JP-A-	3072416	27-03-91
EP-A-0368406	16-05-90	US-A-	5026556	25-06-91
		CA-A-	2002300	10-05-90
		JP-A-	2191214	27-07-90
EP-A-0452837	23-10-91	JP-A-	4001127	06-01-92
		US-A-	5176916	05-01-93

EPO FORM P0479

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82